

High VExUS grades are linked to cardiac function in general intensive care unit patients

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Aims

Even though initially considered as a new standard in systemic venous congestion assessment, the semi-quantitative Doppler ultrasound-based venous excess ultrasound grading system (VExUS) showed inconsistent associations with outcomes in general intensive care unit (ICU) patients. It is unclear why VExUS is so effective in predicting outcomes in some cohorts and not in others. The determinants of higher VExUS have not been studied in a general ICU cohort. The aim of this study was to determine the factors associated with higher VExUS (≥ 2) in a general ICU cohort.

Methods and results

We performed a post-hoc analysis of a prospective, observational cohort, including adult patients within 24 h of ICU admission and expected ICU length of stay longer than 2 days. Collected data included patients' haemodynamic status (including ultrasound evaluation) at several points in time: ICU admission, Day 1, Day 2, Day 5, and the last day of ICU stay. We analysed 514 haemodynamic evaluations in 145 patients. In total, 96/514 (18.7%) had a VExUS grade ≥ 2 . The univariable followed by multivariable mixed-effects logistic regression analyses only found a statistically significant association between VExUS ≥ 2 and right ventricle S wave [OR 0.85 (0.74;0.97), $P = 0.02$] and left ventricle E/A ratio [OR 2.34, 95% CI (1.27;4.33), $P = 0.006$].

Conclusion

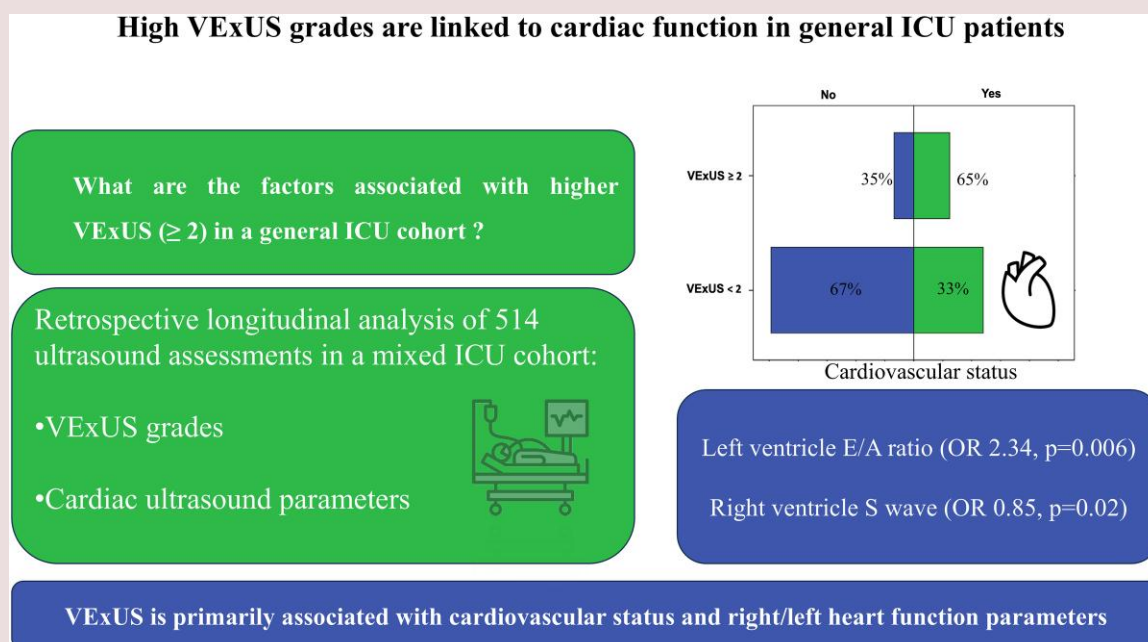
The current study has elucidated that higher VExUS is primarily associated with cardiac comorbidities and ultrasound parameters of left- and right-sided cardiac systolic and/or diastolic function in general ICU patients.

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Graphical Abstract



Keywords

VExUS • Cardiac failure • Cardiac function • ICU • Venous congestion • Sepsis • Ultrasound

Introduction

Venous congestion represents a serious burden in the intensive care unit (ICU) patients, as it can result from multiple common causes, including cardiac failure and fluid overload.¹ The pathophysiology of venous congestion is complex, finally conducting to impaired organ and tissue perfusion and with consequent increase in ICU morbidity and worsened outcomes.^{2,3} Despite its well-acknowledged clinical impact, the appropriate diagnosis and management of venous congestion is still a difficult task in ICU.

There is a continuous struggle to provide maneuverable tools of ICU congestion assessment in research and clinical practice. Based on the extrapolation of cardiology recommendations and congestive cardiac failure, the practitioners commonly use an approach combining clinical, laboratory ultrasound, or X-rays parameters.⁴ However, this approach has its challenges, being sometimes subjective, time-consuming, and less practical in the case of repeated assessments. During the last decade, an increasing interest has been noticed regarding non-cardiocentric haemodynamic paradigm, like the venous ultrasound.⁵ Several biological, haemodynamic, and echocardiographic parameters have been proposed as surrogates of haemodynamic congestion. Based on the available literature, it seems that these parameters may not reflect the same underlying process, thus they may not be inter-changeable. Other parameters were mainly studied during the acute phase of circulatory failure, and it might not be easily extrapolated to the de-escalation phase.⁶ In addition, the lack of standardization across all these parameters and definitions prevents generalization of results and likely explains the discordance between studies.

An elegant and promising solution appeared to be the venous excess ultrasound grading system (VExUS), a semi-quantitative Doppler ultrasound-based assessment of the hepatic vein, portal vein, and intrarenal venous flow, providing a comprehensive overview of the venous

haemodynamic status.⁷ Derived from cardiology and nephrology area, VExUS demonstrated an association with the prevalence of acute kidney injury (AKI) in post-operative cardiac surgery patients and also in patients with acute coronary syndrome.^{8,9} Even though initially considered as a new standard in congestion, VExUS showed inconsistent associations with outcomes in general ICU patients and with different types of AKI.^{10–12} It is unclear why VExUS is so effective in predicting outcomes in some cohorts and not in others. The determinants of higher VExUS, other than congestion, have not been studied, particularly in a general ICU cohort.

The aim of this study was to determine the factors associated with higher VExUS in a general ICU cohort.

Methods

Patients and study design

We performed a post-hoc analysis of a prospective, observational cohort (IRB 2020-A01819-30, CPP Sud Ouest Outre Mer III, ClinicalTrials.gov Identifier: NCT04680728). Data collection was performed in four tertiary ICUs from October 2020 to October 2022. The patient or their kin provided written informed consent for study participation. The study was conducted in accordance with the 1964 Declaration of Helsinki.

We included adult patients within 24 h of ICU admission and expected ICU length of stay longer than 2 days. We did not include (i) person not affiliated to national health insurance, (ii) age < 18 years, (iii) pregnant or breastfeeding women, (iv) poor echogenicity confirmed by the ultrasound operator, (v) chronic atrial fibrillation, and (vi) mechanical cardiac assistance.

Ultrasound measurements

The ultrasound measurements were performed according to the current guidelines. The left ventricular ejection fraction (LVEF) was measured using Simpson's biplane method. The right ventricular systolic function was

assessed by M-mode annular systolic excursion plane [tricuspid annular plane systolic excursion (TAPSE)], measured by placing the M-mode sample volume at the level of the basal right ventricular free wall and by measuring the right ventricular S wave. The supra-hepatic vein systolic (HV-S) and HV-diastolic (HV-D) flow velocities were measured, and the S/D ratio was calculated. The diameter of the inferior vena cava (IVC) was measured in the subcostal view, 1.0 cm from its junction with the right atrium, with the patient in the supine position. The maximum and minimum diameters of the IVC were measured, and the mean IVC diameter was calculated. The portal vein flow pulsatility index (PI) was assessed using pulsed-wave (PW) Doppler in the liver hilum. The maximum velocity (V_{max}) and minimum velocity (V_{min}) of the portal vein were also measured, allowing the calculation of the portal PI with the formula: $PI = (V_{max} - V_{min}) / V_{max}$. The intrarenal venous flow was classified according to the waveform pattern.

The acquisition of ultrasound images was performed by a board-certified physician using the Philips Envisor ultrasound system (Affinity ultrasound system, Philips Medical System, Suresnes, France) and a concomitant ECG. The ultrasound parameters were calculated as the average of five measurements (unless specified otherwise), regardless of the respiratory cycle. Data were acquired, stored, and reviewed offline by an experienced operator blinded to the study outcomes.

Data collection

Patients' demographic characteristics [age, gender, weight, body mass index (BMI)], associated medical conditions, reason for admission, SOFA, and SAPS II scores were collected at inclusion. Collected data included patients' haemodynamic status (including ultrasound evaluation) at several points in time: ICU admission, Day 1, Day 2, Day 5, and the last day of ICU stay. The clinical assessment included haemodynamic parameters [blood pressure, heart rate, central venous pressure (CVP)], use of renal replacement therapy, ventilatory parameters, and catecholamine use.

Study endpoint

The study endpoint was a VExUS ≥ 2 at the time of one ultrasound assessment. We chose type C of VExUS because it was initially associated with AKI and used in other studies. A VExUS ≥ 2 was considered high VExUS as it was initially associated with AKI in cardiac cohort patients.

Statistical analyses

The data are presented as mean ($\pm$ standard deviation), median [25–75% interquartile range], or proportions, as appropriate. The statistical analyses were performed using R software version 3.4.4 (R Foundation for Statistical Computing, Austria) and the library lmerTest. A P -value < 0.05 was considered statistically significant. We performed univariable mixed-effects logistic regression analyses with VExUS ≥ 2 (qualitative) as the dependent variable, each variable of interest as an independent variable (fixed effect), and the patient as a random effect. Secondly, the non-redundant and clinically pertinent variables that showed a statistically significant association in univariable analyses ($P < 0.05$) were included in a multivariable logistic mixed-effects regression analysis. The mixed-effects model addresses the risk of auto-correlation in the case of repeated measurements. We assessed collinearity by calculating the variance inflation factors for the multivariable model. A variance inflation factor > 2 indicated highly correlated predictors.

Results

Patients' characteristics

We analysed 514 haemodynamic evaluations in 145 patients of medico-surgical general ICU. Among them, 14 (10%) had chronic obstructive pulmonary disease, 86 (59%) had high blood pressure, and 49 (34%) had ischaemic heart disease. Additionally, 21 (15%) had chronic systolic heart failure, 37 (26%) had valvular heart disease, and 12 (8%) had peripheral artery disease. Diabetes was managed with oral antidiabetics in 26 (18%) patients and insulin in 15 (10%). Chronic kidney disease and stroke were each present in 15 patients (10%).

A significant portion, 92 patients (63%), were admitted to the ICU for non-surgical reason, with a median SAPS II score of 46 [37;59].

Table 1 Univariable mixed-effects logistic regression analysis with VExUS ≥ 2 as dependent variable (admission characteristics)

Variables	Coefficient (95% CI)	P-value
Age (1 year)	1.01 (0.98;1.04)	0.448
Weight (1 kg)	0.99 (0.97;1.02)	0.992
BMI (1 kg/m ²)	0.98 (0.91;1.06)	0.684
ICU admission		
Admission SAPS2 (1 unit)	1 (0.97;1.03)	0.773
Admission SOFA (1 unit)	0.88 (0.77;0.99)	0.038
ICU admission reason		
• Admission sepsis patient (yes)	0.44 (0.01;2)	0.289
• Admission cardiac patient (yes)	5.34 (2.29;12.5)	<0.001
• Admission neurological patient (yes)	0.5 (0.1;1.8)	0.278
Past medical history		
• High blood pressure (yes)	0.67 (0.27;1.66)	0.39
• Ischaemic heart disease (yes)	2.29 (0.91;5.76)	0.076
• Chronic heart failure (yes)	8.5 (2.7;26.8)	<0.001
• Valvular disease (yes)	8 (3.2;20.3)	<0.001
• Peripheral artery disease (yes)	0.22 (0.03;1.53)	0.127
• Diabetes (yes)	1.57 (0.49;4.95)	0.441
• Chronic kidney failure (yes)	3.8 (0.96;15.1)	0.056
• Stroke (yes)	6.8 (1.8;26)	0.004

Abbreviations: BMI, body mass index; CI, confidence interval; ICU, intensive care unit; SAPS 2, simplified acute physiology score; SOFA, sequential organ failure assessment; VExUS, venous excess ultrasound system.

All the patients were in sinus rhythm at the moment of ICU admission. Sixty-three (43%) and 22 (15%) patients have been treated with vasopressor and/or inotrope, respectively. One hundred twenty-six (88%) patients required mechanical ventilation in ICU with a median PEEP of 6 [5;8] mmHg. Mechanical ventilation at ICU admission was required in 15% of patients admitted for cardiac reason and, respectively, in 82% of patients admitted for non-cardiac reason ($P = 0.001$). Ten (7%) patients required renal replacement therapy in ICU. The median ICU length of stay was 6 [4;13] days.

Among the 514 haemodynamic evaluations, 96 (18.7%) had a VExUS grade ≥ 2 . Of these 96 assessments with VExUS grade ≥ 2 , 29 were at the moment of ICU admission, 26 at Day 1 in ICU, 28 at Day 2 in ICU, 2 at Day 5 in ICU, and 11 were at moment of ICU discharge.

Factors associated with VExUS grade ≥ 2 during the entire intensive care unit stay

Several admission parameters and patients' general characteristics demonstrated an association with VExUS ≥ 2 in ICU in univariable mixed-effects logistic regression analyses (Table 1 and Figure 1): cardiac reason for ICU admission [OR 5.34, 95% CI (2.29;12.5), $P < 0.001$], admission SOFA [OR 0.88, 95% CI (0.77;0.99), $P = 0.038$], personal history of chronic heart failure [OR 8.5, 95% CI (2.7;26.8), $P < 0.001$], personal history of valvular disease [OR 8 95% CI (3.2;20.3), $P < 0.001$], and personal history of stroke [OR 6.8, 95% CI (1.8;26), $P = 0.004$].

The mixed-effects logistic regression analyses evaluating the haemodynamic parameters associated with VExUS ≥ 2 in ICU are presented

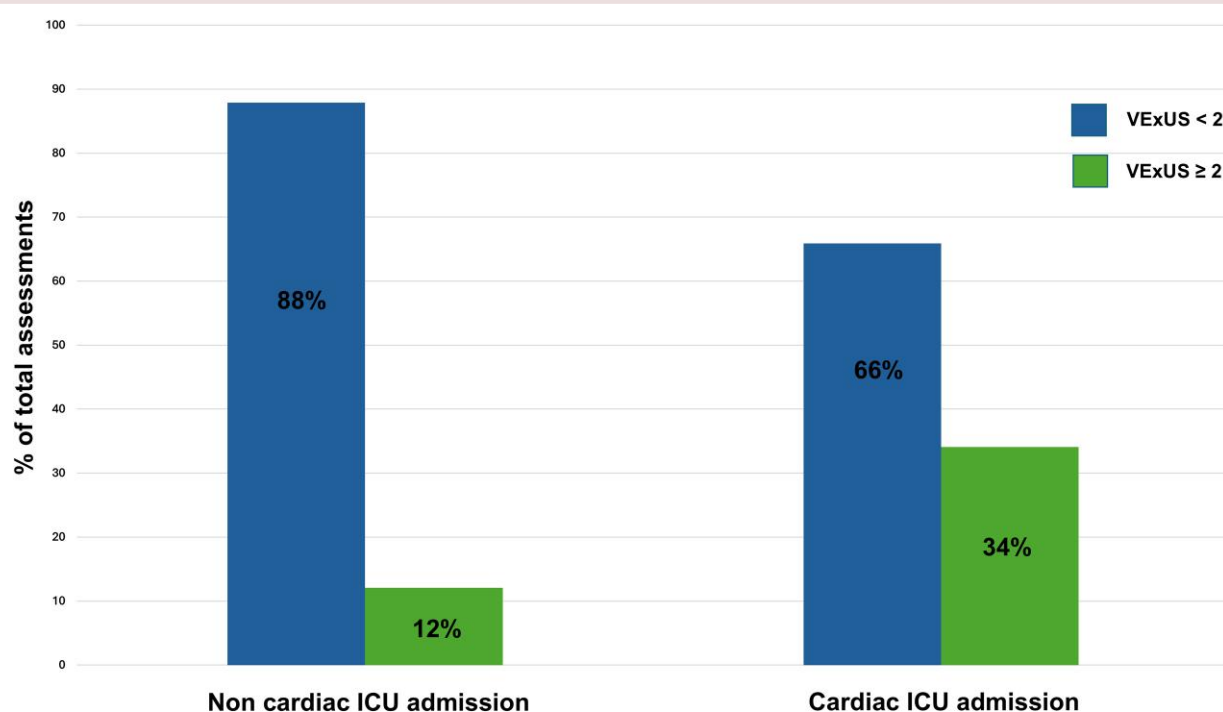


Figure 1 Percentage (%) of assessments with VExUS ≥ 2 and < 2 in patients with/without cardiac reason for ICU admission.

in Table 2. The univariable mixed-effects logistic regression analyses found a statistically significant association between VExUS ≥ 2 and CVP [OR 1.09, 95% CI (1.01;1.19), $P = 0.039$], LVEF [OR 0.97, 95% CI (0.95;0.99), $P = 0.045$], left ventricle E/A ratio [OR 3.01, 95% CI (1.91;4.76), $P < 0.001$], and right ventricle S wave [OR 0.8, 95% CI (0.73;0.88), $P < 0.001$]. The multivariable mixed-effects logistic regression analyses found a statistically significant association between VExUS ≥ 2 and right ventricle S wave [OR 0.85 (0.74;0.97), $P = 0.02$] and left ventricle E/A ratio [OR 2.34, 95% CI (1.27;4.33), $P = 0.006$].

Discussion

This is the first study to demonstrate a clear association between higher VExUS, cardiac comorbidities, and cardiac function in a general ICU cohort. This is a significant and novel finding that may substantially clarify the inconsistencies related to VExUS prognostic function in previous studies. Our findings may explain the inconsistency between prior studies regarding the usefulness of VExUS for assessing congestion in the ICU, suggesting its role particularly in a cardiac context.

The association of VExUS with cardiac comorbidities and condition is not a new finding, as VExUS was developed in a post-cardiac surgery cohort.⁸ It has also demonstrated an association with mortality in cardiac failure patients.¹³ The fact that patients with cardiac dysfunction presented with ultrasound parameters of congestion in the ICU is intuitively expected and has been extensively studied in cardiology. This paradigm can also explain the reported correlation between VExUS and right heart pressures or mean systemic filling pressure in cardiac ICU cohorts.^{2,14,15} In a recent prospective cohort including patients with acute coronary syndromes, Viana-Rojas *et al.* demonstrated an interesting association between higher VExUS and inferior myocardial infarction, comparing with anterior myocardial infarction.⁹ In the case of increased cardiac pressures with normal or altered right ventricle

function (or left ventricle), pathological retrograde venous flow patterns develop, thus altering the different parameters included in VExUS calculation.^{16,17} The close relationship between heart failure and kidney failure (and worsened outcomes) has also been extensively studied in cardiology with different types of cardio-renal syndromes.¹⁸ However, the role of cardiac function in congestion in ICU patients can only describe the cardio-centric paradigm of congestion, which is just one of the existing endotypes.¹⁹

Within the ICU environment, the prevalence of congestion may be augmented by multiple factors: underlying pathologies (such as acute respiratory distress syndrome, renal failure, cirrhosis, sepsis, and cardiac failure), mechanical positive pressure ventilation, and various therapeutic interventions (including fluid administration and blood transfusions), which collectively contribute to disturbances in cardiovascular homeostasis. While differentiating the individual effects of positive mechanical ventilation, fluid status, or congestive cardiac failure based solely on higher VExUS grades may be challenging, the impact of positive mechanical ventilation on VExUS determinants appears low within typical ICU parameters. Studies have demonstrated that positive pressure application significantly increases portal flow pulsatility only at values exceeding 15 cmH₂O, which are uncommon in mixed ICU population.^{20,21} In this sense, mechanical ventilation was not associated with high VExUS grades in the present study. Moreover, studies evaluating VExUS in mechanically ventilated patients without cardiovascular comorbidities have observed low prevalence of high VExUS grades, whereas most published studies reporting high VExUS grades were systematically conducted in non-mechanically ventilated cardiac patients.^{8–10,14,15,19,22–24} Regarding volume status, VExUS only increases following an increase in preload in patients suffering of heart failure.^{25,26} Finally, Wong *et al.*, in their study in patients with end-stage renal failure undergoing fluid-removal haemodialysis, demonstrated that higher VExUS is more indicative of right and/or left ventricular dysfunction than venous volume status.²² In our general ICU cohort, higher

Table 2 Univariable mixed-effects logistic regression analysis with VEXUS ≥ 2 as dependent variable

Variables	Univariable Odd ratio (95% CI)	P-value	Multivariable Odd ratio (95% CI)	P-value
<i>Haemodynamic parameters</i>				
• Clinical examination				
MAP (1 mmHg)	1.01 (0.99;1.04)	0.334		
CVP (1 mmHg)	1.09 (1.01;1.19)	0.039	1.03 (0.94;1.14)	0.438
Oedema				
• Mild oedema (yes)	1.32 (0.5;3.3)	0.547		
• Moderate oedema (yes)	1.2 (0.37;3.6)	0.802		
• Severe oedema (yes)	1.03 (0.26;4.1)	0.966		
Oedema binary (yes)	1.2 (0.6;2.6)	0.609		
Cumulated fluid balance (1 mL/kg)	0.99 (0.98;1)	0.398		
Inotrope use (yes)	1.61 (0.26;10.1)	0.608		
Inotrope dose (1 mcg/kg/min)	1.04 (0.77;1.41)	0.258		
Vasopressor use (yes)	1.67 (0.75;3.72)	0.205		
Vasopressor dose (1 mcg/kg/min)	1.36 (0.63;2.93)	0.792		
Diuretic use (yes)	0.94 (0.63;1.4)	0.752		
RRT (yes)	0.7 (0.1;4.3)	0.675		
Mechanical ventilation (yes)	0.61 (0.3;1.3)	0.198		
• Laboratory parameters				
Haemoglobin (1 g/dL)	1 (0.82;1.23)	0.948		
Haematocrit (1%)	1 (0.94;1.07)	0.928		
Sodium (1 mmol/L)	0.98 (0.95;1.01)	0.219		
Creatinin (1 mcmol/L)	1 (0.99;1.01)	0.051		
Proteins (1 g/L)	0.99 (0.95;1.03)	0.832		
Albumin (1 g/L)	1 (0.97;1.03)	0.865		
Lactates (1 mmol/L)	0.95 (0.78;1.15)	0.596		
NT-pro-BNP (1 pmol/L)	1 (0.99;1)	0.677		
• Echocardiography parameters				
RV S wave (1 mm)	0.8 (0.73;0.88)	<0.001	0.85 (0.74;0.97)	0.02
TAPSE (1 mm)	1 (0.98;1.03)	0.475		
LVEF (1%)	0.97 (0.95;0.99)	0.045	1 (0.97;1.04)	0.778
MAPSE (1 mm)	1.07 (0.99;1.16)	0.083		
LV E/E' ratio	1.04 (0.97;1.11)	0.233		
LV E/A ratio	3.01 (1.91;4.76)	<0.001	2.34 (1.27;4.33)	0.006
LV 4 chambers diameter (1 cm)	0.95 (0.8;1.13)	0.591		
RV 4 chambers diameter (1 cm)	0.97 (0.66;1.46)	0.907		

Abbreviations: CI, confidence interval; CVP, central venous pressure; MAP, mean arterial pressure; LV, left ventricle; LVEF, left ventricle ejection fraction; MAPSE, mitral annular plane systolic excursion; NT-pro-BNP, N-terminal brain natriuretic peptide; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; RRT, renal replacement therapy; VExUS, venous excess ultrasound grading system.

VExUS was also noted both in patients with cardiac comorbidities and in patients with persistent alterations in parameters related to cardiac systolic and diastolic function. The association with cardiac function parameters of a higher VExUS should be considered in the context of a rather lower prevalence of significant congestion (assessed using VExUS) in this general ICU database.¹¹

Our study yielded results that, while initially appearing unexpected, align with existing research and offer valuable insights. Some observed associations may seem surprising at first glance, but they can be explained by several factors, particularly the nature of our studied

population—a mixed ICU cohort with a low prevalence of cardiovascular alterations phenotypes.¹⁹ Previous research has demonstrated that the E/A ratio may be a more robust parameter than the E/e' ratio to assess ventricular filling pressure.^{27–30} Moreover, the E/e' ratio is more prone to measurement errors than the E/A ratio.³¹ As we studied a mixed ICU cohort with low prevalence of high ventricular filling pressure, E/A ratio may have been more sensitive than E/e' ratio. Consequently, current guidelines recommend using multiple parameters to evaluate ventricular filling pressure comprehensively.³² We observed a significant association between VExUS and RV S' wave in

this cohort, but not with TAPSE. Other authors have already pointed out some differences between S' wave and TAPSE in assessing right ventricular function. In one study, S' wave was more easily obtainable and demonstrates greater reproducibility compared with TAPSE.³³ Additionally, S' was less influenced by preload and afterload variations than TAPSE.³⁴ The observed difference requires cautious interpretation, as the lack of association between TAPSE and VExUS in our cohort may be attributed to several unassessed factors beyond the scope of the study.

Our study results provide important arguments regarding the possibly less useful role of VExUS in non-cardiac causes of congestion in the ICU (other congestion endotypes)¹⁹ and a robust explanation for the inconsistencies in VExUS research findings. In the pathophysiological mechanism of peripheral congestion development in the ICU, the clinical presentation might not initially be associated with cardiac function alterations or IVC distension (although these features can also be present in later stages), thus with increased VExUS (because its calculation relies on IVC distension)^{19,35} Some individualized venous ultrasounds or clinical parameters, related to the splanchnic reservoir or peripheral congestion (i.e. portal PI), might be of more interest in this particular congestion endotype. In a cohort of septic shock patients, Fujii *et al.* found that the intrarenal venous discontinuous flow from Doppler ultrasonography was associated with AKI, but not with CVP.³⁶ In this way, one can understand why the portal PI demonstrated its usefulness where VExUS seemed to fail.²⁴

The clinical relevance is that VExUS should be used to assess congestion and to predict outcomes mainly in the context of cardiac right and/or left-sided failure.³⁷ Not all the phenotypes of congestion existing in ICU patients might be well-assessed using VExUS. However, further tools need to be explored in systemic (peripheral) congestion of non-cardiac origin.

Limitations

This study has several limitations. Firstly, it was an unplanned, post-hoc, retrospective analysis of a prospectively collected observational cohort. Secondly, the differentiation between the congestion endotypes might not be clear, with possibly intricate mechanisms and features. Even defining congestion is challenging, lacking a gold standard definition. Thirdly, the longitudinal analysis provided an overview of the entire ICU stay. However, most ultrasound assessments were performed within the first 72 h of ICU admission and on the last day in ICU. Some other time points in the ICU might have been missed. Also, even though we considered the main therapeutic interventions, we could not take into account the entire patients' management heterogeneity in such general ICU cohort. Fourthly, useful ultrasound or invasive parameters for a more advanced assessment of the cardiac function were not measured (e.g. tricuspid regurgitation assessment, right ventricle—pulmonary artery coupling, speckle-tracking imaging, etc.). Both TAPSE and S', which assess the longitudinal motion of the basal lateral free wall of the RV, have inherent limitations in the presence of regional variations in contraction.³³ Our statistical approach warrants discussion. We constructed the multivariate model based on univariate statistical significance, though alternative methods exist.³⁸ The study aimed to explain rather than predict higher VExUS grades,³⁹ resulting in a parsimonious, clinically relevant model without significant collinearity. We did not adjust for multiple comparisons, potentially increasing type I error risk. However, this approach avoided inflating type II error risk,⁴⁰ and our findings remained clinically coherent.

Conclusion

The current study has elucidated that higher VExUS is primarily associated with cardiac comorbidities and ultrasound parameters of left- and right-sided cardiac systolic and/or diastolic function. Other

parameters should be considered in cases of congestion of non-cardiac origin or with less cardiac impact. Further studies are needed to clarify the role of venous congestion parameters in assessing the various ICU congestion endotypes.

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None

Authors' contributions

Conception and study design: S.A., M.N., B.B., P.G.G. Data collection: S.A., M.N., B.B., P.G.G. Statistical analysis: S.A., P.G.G. Interpretation of data: S.A., B.B., P.G.G. Writing up the first draft of the paper: S.A., P.G.G. Critical revision of manuscript: M.N., B.B. Final approval of the manuscript: all authors.

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Ethical approval

The CODOREA study protocol received the approval of an independent ethics committee (IRB 2020-A01819-30, CPP Sud Ouest Outre Mer III, ClinicalTrials.gov Identifier: NCT04680728). All patients or their kin received a written information letter and gave consent to participate. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Conflict of interest: None declared.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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